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Review Article

Toxic Ties: The Physicochemical Impact of Tobacco on Oral Health- A comprehensive review

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ABSTRACT:
This review article provides a comprehensive analysis of the physicochemical relationship between tobacco use and oral lesions. Both smoking and chewing tobacco contribute to an increased risk of oral cancer by disrupting the balance between free radicals and antioxidants. A premalignant lesion refers to a cellular alteration with a higher-than-normal risk of malignant transformation. While oral precancerous conditions are routinely evaluated and managed as part of standard oral healthcare, some controversies persist. A significant advancement in this field is the recognition that not all premalignant lesions necessarily progress to malignancy. Cancer is the second leading cause of death worldwide, surpassed only by cardiovascular diseases. It is estimated that tobacco use accounts for 90% of oral cancer cases. This article provides a thorough review of tobacco-related oral lesions.
Keywords: Oral mucosa, Tobacco, Precancerous lesion, Oral cancer, Physiochemical reaction, Adverse effects

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INTRODUCTION

Tobacco was first introduced to Europe by Spanish and Portuguese explorers of America in the early 16th century. The method of tobacco consumption significantly influences the appearance, location, and frequency of associated lesions. In Western countries, cigarettes, cigars, and pipes are the primary forms of tobacco use. However, smokeless tobacco products, such as chewing tobacco and snuff dipping, have gained popularity in recent years. [1].

Although tobacco is widely recognized as a major etiological factor in leukoplakia, epithelial dysplasia, and squamous cell carcinoma, several other tobacco-related lesions have also been identified. The primary non-malignant oral lesions associated with tobacco use are categorized under dental, gingival, and mucosal conditions. The composition of tobacco is mentioned in the tabular column 1[2]

Table: 1 COMPOSITION OF TOBACCO AND ITS BY PRODUCTS

Constituent	Minimum	Maximum	~ Fold Difference
Nicotine, mg/g	5.5	2.8	15.5
Unprotonated nicotine, mg/g	0.008	9.2	1,200
NNN, µg/g	0.5	13.0	26
Nornicotine, mg/g	0.07	0.6	8.6
Nitrite, µg/g	0.5	543	1,100
Benzo(a)pyrene, ng/g	13	86	6.6
Cadmium, µg/g	1.2	1.9	1.6
Formaldehyde, µg/gg	10.6	1.6	6.6

Effect of nicotine

Nicotine, an alkaloid naturally found in solanaceous plants such as potatoes, tomatoes, green peppers, and tobacco, is linked to individual smoking habits due to genetic variations in its metabolism. The production of hydroxyl free radicals contributes to various toxic reactions. Increased levels of superoxide and hydrogen peroxide can damage alveolar macrophages, triggering the release of harmful proteolytic enzymes. Additionally, nicotine stimulates the release of lactate dehydrogenase, leading to mucosal membrane damage.[3]

Furthermore, nicotine induces apoptosis and oxidative stress while exhibiting genotoxic effects by causing chromosomal aberrations and promoting cell proliferation. These biological and molecular changes, driven by nicotine's chemical properties, play a role in cancer development. [4]

Effect of unpronated nicotine

Nicotine, the primary addictive component in tobacco, exerts its effects based on its bioavailability, which is determined by the proportion of its total content present in the unprotonated form. [5] In Smokeless Tobacco products, the unprotonated nicotine content is highly influenced by even slight variations in the product ph.

Effect of nitrite and nitrate

The carcinogenic effect of chewed tobacco is most evident at sites where the tobacco quid is held for an extended period. In this study, salivary nitrate and nitrite levels showed no significant difference between men and women. The majority of oral carcinoma patients in this study were elderly, falling within the age range of 35–70 years, with an average age of 45 years. Additionally, the rate of salivary nitrate-to-nitrite reduction was significantly higher in oral carcinoma patients compared to healthy individuals and those with oral submucous fibrosis (OSMF).[6]

Effect of nornictotine

The minor tobacco alkaloid nornicotine can be readily nitrosated in human saliva, leading to the formation of N'-Nitrosonornicotine (NNN), a potent carcinogenic nitrosamine. Nornicotine is found in tobacco, cigarette smoke, and, as demonstrated in this study, in oral nicotine replacement therapy (NRT) products such as nicotine gum and lozenges. Nitrate, naturally present in human saliva, is converted to nitrite by oral microflora. As a result, NNN can be endogenously formed in users of oral NRT products, as well as potentially in smokers and smokeless tobacco users.[7]

The use of deuterium-labeled precursors enabled us to specifically identify NNN formed from the precursors added to saliva before incubation. This approach eliminated concerns that the NNN detected in the saliva of our non-smoking volunteers may have originated from other source [8]

The minimal nitration of [pyridine-D4]nicotine observed during saliva incubation experiments aligns with kinetic studies demonstrating that nornicotine undergoes nitrosation to form NNN much more efficiently than nicotine. These findings further suggest that nornicotine, rather than nicotine, is the primary precursor of endogenously synthesized NNN in some users of oral NRT products.

Effect of NNN

NNN is believed to play a crucial role in the development of cancer associated with smokeless tobacco products, all of which share a common feature: the presence of both nicotine and NNN. Nicotine is the addictive component found in all tobacco products, including smokeless tobacco. NNN, the primary carcinogenic compound in smokeless tobacco, is structurally similar to nicotine and is known to induce cancers of the oral cavity and esophagus.

Nicotine is metabolized by cytochrome P450 2A6 (CYP2A6) at its 5'-position to form α-hydroxynicotine, which exists in equilibrium with the nicotinium ion. These compounds are further oxidized by aldehyde oxidase and CYP2A6 to produce cotinine, the primary metabolite of nicotine. Notably, the nicotinium ion does not react with DNA.

Similarly, NNN undergoes metabolism at its 5'-position by CYP2A6 and CYP2A13, leading to the formation of 5'-hydroxyNNN. This highly reactive intermediate undergoes ring opening to form a diazohydroxide, which readily interacts with DNA, creating adducts that can cause miscoding during DNA replication. This process ultimately results in permanent mutations and, over time, the development of cancer.

The DNA adducts formed from diazohydroxide intermediates generated during NNN metabolism have been extensively studied in rats treated with NNN. These adducts arise from both 2'-hydroxylation and 5'-hydroxylation of NNN, further supporting its role in carcinogenesis. [9]

Oral lesions

Dental Conditions

A dark brown to black discoloration along the cervical margins of teeth, caused by tar and other combustion by-products, is commonly associated with smoking. Additionally, extrinsic staining from dietary substances such as coffee and tea may contribute to this discoloration. A history of tobacco use is crucial in determining the correct diagnosis and etiology. While these deposits are primarily an aesthetic concern, they can also facilitate plaque accumulation.[10]

Abrasion from pipe smoking typically affects the occlusal surfaces due to the placement of the pipe stem, whereas abrasion from smokeless tobacco

primarily occurs on the vestibular surface opposite the tobacco wad. However, if the tobacco is chewed, the occlusal surfaces may also be involved. This abrasion can lead to dentin hypersensitivity, pulp exposure, or apertognathia (open bite). In pipe smokers, apertognathia usually develops unilaterally on their preferred smoking side. Individualized treatment options may include dentin desensitization, endodontic therapy, and crown placement. [11][12]
Among smokeless tobacco users, there is an increased gingival recession with exposure of tooth root surface, periodontal pocket formation, plaque and calculus accumulation which leads to periodontitis.

Gingival Conditions
Acute necrotizing ulcerative gingivitis (ANUG) is a painful and rapidly progressive disease of the free gingiva, attached gingiva and alveolar mucosa characterized by necrosis of the gingival papilla accompanied by halitosis. ANUG primarily affects young adults who smoke heavily and have poor oral hygiene.
Although the exact interaction between ANUG and smoking is not clear, local and systemic effects have been suggested. The progression of ANUG may be enhanced by plaque accumulation in sites with tar deposits and tissue ischemia secondary to nicotinic vasoconstriction.[13]
The prevalence of periodontitis is greater in smokers than non-smokers' and the alveolar bone is more susceptible to resorption in smokers. Smoking has been implicated in impairing normal host immunity in terms of neutralizing infection.[14]
Cigarette smoking has been linked to impaired healing and reduced improvement in pocket depth following simple pocket-reduction surgery. Smoker's melanosis, affecting approximately 25% to 31% of tobacco users, is characterized by discrete or coalescing brown macules. These lesions most commonly appear on the attached mandibular gingiva on the labial side, though pigmentation of the palate and buccal mucosa has also been observed, particularly in pipe smokers.[15]
Other entities to consider in differential diagnosis are racial melanosis, melanosis due to medications, Peutz-Jegher's syndrome, Addison's disease and early melanoma. [16] Smoker's melanosis is benign and not considered to be precancerous, but a biopsy may be indicated to rule out more serious conditions, in particular melanoma. A gradual return to normal pigmentation over several months to years has been reported following smoking cessation.

Mucosal Conditions
Burns and keratotic patches frequently develop on the lips at the site of habitual cigarette smoking, especially when a cigarette or cigar is held as a stub for extended periods. These lesions typically appear on the mucosal surfaces of the upper and lower lips where the cigarette is placed. They are characterized by flat or slightly elevated whitish areas with red striations. The primary treatment recommendation is smoking cessation.[17]
Lesions caused by smokeless tobacco typically exhibit a wrinkled surface, varying in appearance from opaque white to translucent, and are found at the site where the snuff is placed. Additionally, hypertrophy of the filiform papillae and a slowed rate of desquamation on the dorsal surface of the tongue create a hair-like appearance. [18]
Black hairy tongue is most commonly observed in heavy smokers. Clinically, it typically originates near the foramen cecum and extends anteriorly and laterally, with elongated filiform papillae that can grow several millimeters in length. Although usually asymptomatic, some individuals may experience a gagging or tickling sensation if the papillae become excessively long.
Nicotinic stomatitis occurs almost exclusively in heavy pipe smokers and rarely in cigarette or cigar smokers.[16]This condition typically appears as redness on the palate, located posterior to the rugae. Over time, it develops a grayish-white, nodular appearance due to periductal keratinization of the minor salivary glands. A distinctive feature is the presence of multiple red dots, which represent dilated and inflamed duct openings of the minor salivary glands. It is caused by local exposure to thermal and chemical agents. Nicotinic stomatitis is not considered a precancerous lesion. [19][20]
In addition to nicotinic stomatitis, heavy smoking can cause painful palatal erosions. These erosions result from prolonged exposure to elevated temperatures in the oral cavity.

Precancerous lesion and Oral cancer
Numerous studies have demonstrated that tobacco use can lead to the abnormal expression of genes such as p53, GLUT-1, p16, DAPK, MGMT, and P13K in the oral epithelium, which is closely linked to the development of oral squamous cell carcinoma (OSCC). Immune dysfunction plays a crucial role in enabling cancer cells to evade immune responses, facilitating their initiation, progression, and establishment within the body.[21]
Free radicals encompass reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive oxygen metabolites, including hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), hydroxyl radicals (OH^-), nitric oxide (NO), and malondialdehyde. These reactive molecules can cause various forms of DNA damage, such as strand breakage, DNA-protein cross-linking, and base modifications. Additionally, they contribute to lipid peroxidation by interacting with fatty acids in the cell membrane.[22]
The risk of developing oral cancer in smokers was found to be significantly higher than in non-smokers, as indicated by alterations in erythrocytic glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), and plasma thiol levels.[23]

These theories contribute for the development of precancerous lesions and oral cancer in patients addicted to tobacco through molecular pathogenesis.

CONCLUSION

Tobacco, in its various forms, is the leading preventable cause of death and disease. It is a well-established risk factor for oral cancers and precancerous lesions. Additionally, tobacco use contributes to a variety of oral lesions that are not classified as precancerous, yet misinterpreting them may lead to unnecessary cancer-related anxiety.

All oral mucosal lesions in tobacco users should be carefully examined, accurately diagnosed, and correlated with their habits. Long-term follow-up is essential for proper monitoring. Therefore, a thorough understanding of tobacco-related lesions is crucial for differential diagnosis and effective patient management.

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